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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,718	02/12/2002	Allan Y. Chen	693243-76 (UCD-1120)	1621

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,718	CHEN, ALLAN Y.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on January 26, 2004 have been received and entered into the application.

Action Summary

Claims 23-33 of record are rejected under 35 U.S.C. 112, first Paragraph is maintained for the reasons stated in the previous office action.

Claims 23-39 are rejected under 35 U.S.C. 103 (a) over Chen et al. (1997) in view of Prudhomme (2000) is maintained for the reasons stated in the previous office action.

Response to Arguments

Applicant's arguments filed on January 26, 2004 have been fully considered but they are not persuasive. Applicant essentially argues that one skilled in the art is enabled to use the present invention for the treatment of various neoplastic growth because indolocarbazole derivatives in combination with radiation can be used to treat any neoplastic growth and the specification also lists several examples of neoplastic growth including prostate cancer, bone tumor, colon cancer, lymphoma, and brain tumor. This is not persuasive because the rejected claims are drawn to **any** "neoplastic growth". Given the broadest interpretation of the claiming "neoplastic growth" would

encompasses any growth including any benign polyp or a wart that have different known treatment. Only working Example provided by the Applicant is for the specific cancer (breast cancer). Therefore Applicants' claimed any "neoplastic growth" is not enabled by the instant Application.

Applicant next argues that just because camptothecin derivatives are DNA topoisomerase I targeted drugs and can induce radiosensitization, it does not necessary mean that all DNA topoisomerase I targeted drugs can induce radiosensitization. This is not persuasive because each of the components are well known to inhibit specific cancer. Applicant's attention is drawn to Prudhomme reference, Table 10 where it teaches the anti tumor activity of idolocarbazole derivatives for the specific cancer therein. In addition, the treatment of various cancers employing radiation therapy is well known in the art and it is generally combined with chemotherapy as taught by Chen et al. Applicant asserts the mechanism of radio sensitization induced by camptothecin derivatives and indolocarbazole derivatives remains largely unknown and could be totally different. However, the active ingredient gives the pharmacological effect (treating specific cancer) does not alter the fact that the compound has been previously used to obtain the same pharmacological effects which would result from the claimed method by combining well known radiation therapy for the very same utility. One of ordinary skill in the art would have been motivated to combine radiation therapy with idolocarbazole derivatives for the treatment of specific cancer in order to achieve at least an additive effect in treatment of cancer as the combination method is well known by Chen et al.

Applicant further argues that some subclasses of indolocarbazole derivatives are potent inducers of topoisomerase I mediated DNA damage and cytotoxicity, however they fail to have any significant effect in inducing radiosensitization. This is not persuasive because it would have been obvious to one of ordinary skill in the art to employ indolocarbazole derivatives in combination with radiation therapy because the fact that they are potent inducers of topoisomerase I mediating DNA damage and cytotoxicity, and because, they have an effect in inducing radiosensitization whether the effect is significant, in order to achieve at least an additive effect for the well known combination of radiation and chemotherapy method as disclosed by Chen et al. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

In view of the above Office Action of 10/21/2003 is deemed proper and asserted with full force and effect herein to obviate applicant's claims.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 23-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the "treatment of a neoplastic growth of **breast cancer**", does not reasonably provide enablement for the "treating a neoplastic growth". The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

3. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the prior art, state of the prior art and the amount of experimentation necessary. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: All of the rejected claims are drawn to a method of treating a neoplastic growth comprising administrating an indolocarbazole derivative having the structure A and radiation. The nature of the invention is extremely complex in that it encompasses the actual treatment of any neoplastic growth such that the subject treated with above structures does not develop a neoplastic growth.

Breath of the Claims: The complex of nature of the claims greatly exacerbated by breath of the claims. The claims encompass to a method of treating a complex cell proliferation in need of such treatment which has potentially many different causes (i.e. many different mutations or combination of mutations). Each of which may or may not be addressed by the administration of the claimed combination.

Guidance of the Specification: The guidance given by the specification as to how one would administered the claimed compounds to a subject in order to actually treat any neoplastic growth is minimal. All of the guidance provided by the specification is directed towards treatment related to neoplastic growth of breast cancer rather than treatment of any neoplastic growth.

Working Examples: All of the working examples provided by the specification are directed toward the treatment related to neoplastic growth of breast cancer rather than treatment of any neoplastic growth.

State of the Art: While the state of the art is relatively high with regard to treatment of cell proliferation disorders (i.e. specific cancer), the state of the art with regard to treatment of any neoplastic growth is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a structure similar to the claimed structure was administered to a subject to treat development of any neoplastic growth.

Predictability of the Art: The lack of significant guidance from the specification or prior art with regard to the actual treatment of any neoplastic growth in a subject with the claimed structures in combination makes practicing the claimed invention unpredictable in terms of treating any neoplastic growth.

The amount of Experimentation Necessary: In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the

claimed structures in combination with radiation and test the combination in the model system to determine whether or not the combination is effective for treating any neoplastic growth. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard to treatment of any neoplastic growth with any combination, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding treating a neoplastic growth with any combination, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat any neoplastic growth in a subject by administration of one of the claimed combination.

Therefore, a method of treating a neoplastic growth comprising administering combination comprising structure A is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (1997) in view of Prudhomme (2000).

Chen et al. teach that the role of DNA topoisomerase I as a biochemical mediator of radiosensitization in cultured mammalian cells by campotothecain derivatives and it was found that campotothecin enhanced the cytotoxicity of radiation in a schedule-dependent manner by interaction with DNA topoisomerase I. Chen et al. also teach that DNA topoisomerase I, the major cytotoxic target of camptothecin derivatives, was proposed to play a pivotal role in inducing radiosensitization in cells. Chen et al. also demonstrated that mammalian DNA topoisomerase I mediated the enhancement of radiation cytotoxicity. Chen et al. suggest a potential development of topoisomerase I drugs as radiosensitizer in treating human malignancies. Chen et al. teach that the combination of chemotherapy and radiation therapy has become the treatment of choice for a number of advanced human malignancies. Chen et al. teach that a number of

chemotherapeutic drugs are known to be able to synergistically enhance the cytotoxicity of ionizing radiation.

Prudhomme teaches that rebeccamycin analogues are an antitumor agent and they inhibit the activity of topoisomerase. Prudhomme teaches that rebeccamycin analogues exhibit potent inhibitory potencies against topoisomerase I. Prudhomme teaches rebeccamycin analogues have an antitumor activity agonist gastric, colorectal breast, liver and lung cancer. (table 10).

The primary reference does not teach the rebeccamycin analogues in combination with radiation.

It would have been obvious to one of ordinary skill in the art to replace rebeccamycin analogues in place of campotothecin because that rebeccamycin analogues are antitumor agent and they too inhibit the activity of topoisomerase like campotothecin. One of ordinary skill in the art would have been motivated to make such a modification with reasonable expectation of success to provide enhanced cytotoxicity of radiation in with rebeccamycin analogue posing same mechanism as campotothecain (i.e. topoisomerase I inhibition) which is pivotal in enhancement of radiation cytoxicity. Absent any evidence to contrary, there would have been reasonable expectation of successfully treating neoplastic growth comprising administration of rebeccamycin and radiation since the combination of chemotherapy and radiation therapy has become the treatment of choice for a number of advanced human malignancies and a number of chemotherapeutic drugs are known to be able to synergistically enhance the cytotoxicity of ionizing radiation as taught by Chen et al.

Further, there is a suggestion of a potential development of topoisomerase I drugs as radiosentizier in treating human malignancies by Chen et al. It is noted that rebeccaymycin analogue and radiation therapy have common utility of having antitumor activity. One of ordinary skill in the art would have been motivated to employ a potent topoisomerase I drug such as rebeccamycin with radiation in treating human malignancies in a method taught by Chen et al. The amounts of active agents to be used at a noncytotoxic level is obvious because the combination of topoisomerase inhibitor I and radiation treatment provided enhanced cytotoxicity effect as taught by Chen et al. One of ordinary skill in the art would be motivated to use reduced amounts of the active agent to avoid unnecessary extra dosage of potent chemotherapeutic agents. For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Travers
Primary Examiner
Art Unit 1617

Jmk
April 30, 2004